



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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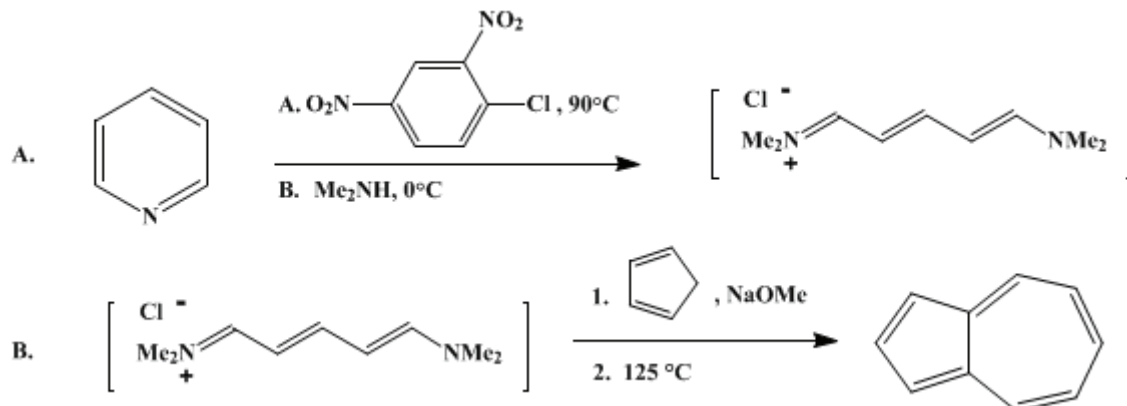
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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AZULENE



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1. Procedure

A 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 500-mL pressure-equalizing dropping funnel, thermometer, and reflux condenser provided with a calcium chloride drying tube is charged with 202.6 g (1.0 mol) of 1-chloro-2,4-dinitrobenzene (Note 1) and 1.2 L of dry pyridine (Note 2). The mixture is heated while it is stirred in a water bath to 80–90°C for 4 hr, during which time a thick yellow precipitate of *N*-(2,4-dinitrophenyl)pyridinium chloride is formed (Note 3). After cooling to 0°C a solution of 100.0 g (2.22 mol) of dimethylamine in 300 mL of dry pyridine was prechilled to 0°C and added dropwise over a period of about 30 min with stirring. The resulting brownish-red liquid reaction mixture is allowed to warm to room temperature and stirring is continued for 12 hr. The drying tube is replaced by a gas inlet and the system is flushed with dry nitrogen in a hood. Under nitrogen, 70.0 g (1.06 mol) of ice-cold, freshly distilled cyclopentadiene (Note 4) is added, and subsequently 400 mL of 2.5 M sodium methoxide solution (Note 5) is slowly added dropwise to the stirred reaction mixture. During addition of the sodium methoxide, the temperature rises to 35–40°C. After the addition is completed, stirring is continued for another 4 hr. The reaction vessel is immersed in an oil bath, the dropping funnel removed, and the flask is fitted with a distillation head. The stirred mixture is cautiously heated under nitrogen (Note 6), and a mixture of pyridine and methanol is distilled off until the temperature of the reaction mixture has increased to 105–110°C (Note 7). After the distillation head is removed and 1 L of dry pyridine added, the black mixture is heated with stirring under a nitrogen atmosphere for 4 days with a bath temperature of 125°C. It is then cooled to 60°C, the reflux condenser is replaced by a distillation head, and pyridine is removed under reduced pressure (Note 8). The gummy black solid residue is removed by a spatula and rinsed with hexanes. It is extracted in a Soxhlet apparatus with 1.5 L of hexanes in several batches. To remove the remaining pyridine, the combined blue hexane rinse and the extraction solutions are carefully washed with two 150-L portions of 10% aqueous hydrochloric acid, then water (Note 9). The organic layer is dried with anhydrous sodium sulfate, the drying agent is removed by filtration, and the solvent is distilled through a 50-cm vacuum-jacketed Vigreux column. The crude azulene is purified by chromatography on activity II alumina (Note 10) with hexane and yields azulene as blue plates, mp 96–97°C, yield 65–75 g (51–59%) (Note 11).

2. Notes

- Commercial 1-chloro-2,4-dinitrobenzene was obtained from Aldrich Chemical Company, Inc. (Milwaukee) or from Bayer, AG (Leverkusen, FRG) and used directly.
- Commercial pyridine was dried over potassium hydroxide or calcium hydride and distilled prior to use. The checkers used reagent-grade pyridine (Mallinckrodt AR), which was distilled from KOH and stored over Linde 4A molecular sieves.

3. The reaction mixture should be evenly warmed to 80–90°C within 30 min with efficient mechanical stirring to prevent caking or "hot spots."
4. **Dicyclopentadiene**, obtained from the Aldrich Chemical Company, Inc. (or E. Merck, Darmstadt, FRG), was cracked just prior to use according to the procedure of Fieser and Williamson,² to give the monomer, bp 40–42°C.
5. **Sodium methoxide** was prepared just prior to use from 23.0 g (1.0 g-atom) of **sodium** metal and 400 mL of anhydrous **methanol** (distilled from **magnesium turnings**), then cooled to room temperature.
6. *Caution!* **Dimethylamine** is evolved.
7. Approximately 600 mL of distillate will be collected.
8. The blue **pyridine** distillate is redistilled through a 50-cm vacuum-jacketed Vigreux column (to avoid loss of **azulene**) until approximately 1.7 L is collected; the residual **azulene** is combined with the main residues for extraction.
9. A total volume of 2 L of **hexane** washes results, accompanied by the gradual precipitation of a yellow solid from the **hexane** washes. The acid-wash procedure frequently leads to emulsions and gummy yellow solid in both phases; back-extraction of the "aqueous" layer with **hexane** may be necessary.
10. Alumina was purchased from Macherey, Nagel and Co., Düren [Federal Republic of Germany (FRG)]. The checkers employed 650 g of neutral alumina (Fisher, adsorption grade, 80–200 mesh) packed in a 40-cm-high column. Yellow impurities remained on the column, while the blue **azulene** came off with the **hexane** solvent front.
11. Further purification of **azulene** may be achieved by sublimation at reduced pressure, mp 99°C.^{3,4} The checkers found that mechanical losses, particularly as mentioned in (Note 9), lead to reduction in yield with reduction in scale (0.1 mol, 39% yield; 0.5 mol, 43% yield; 0.8 mol, 79% yield).

3. Discussion

Azulene has been synthesized by a variety of methods: by dehydrogenation of hydroazulenes,^{3,4} by annelation of a seven-membered ring on a five-membered ring either by ring-closure of vinylogous aminopentafulvenes,^{5,6,7} or by cycloadditions of aminopentafulvenes with activated 1,3-dienes or alkynes,^{8,9,10,11} and by annelation of a five-membered ring on a seven-membered ring starting from troponoids or heptafulvenes.^{12,13,14,15,4} Of these, the Ziegler–Hafner synthesis of **azulene**^{5,6} by thermal cyclization of the 6-(4-methylanilino-1,3-butadienyl) pentafulvene proved to be the most versatile. **Azulene** is also simply prepared from 6-dimethylaminopentafulvene and **thiophene 1,1-dioxide** or from 6-acyloxypentafulvenes and **1-diethylaminobutadiene**, but with lower yields.^{9,11,e}

The present procedure, based on the Ziegler–Hafner synthesis, is simple and avoids the use of **benzidine** for the ring closure of the pentafulvene and isolation of the 5-dimethylamino-2,4-pentadienyldenedimethyliminium perchlorate.^{16,17} Other amines were also checked; with **N-methylaniline**, ring closure of the resulting pentafulvene in **pyridine** failed; and with **diethylamine**, a delay in boiling can take place during the reaction.

Substituted azulenes can be prepared in the same manner by the use of substituted cyclopentadienes or substituted pentamethinium salts.

References and Notes

1. Institut für Organische Chemie der Technischen Hochschule, Petersenstr. 22, D-6100 Darmstadt (FRG).
2. Fieser, L. F.; Williamson, K. L. In "Organic Experiments," 3rd ed.; D. C. Heath and Co.: Lexington, MA, 1975; pp 118–120.
3. Treibs, W.; Kirchhof, W.; Ziegenbein, W. *Fortschr. Chem. Forsch.* **1955**, 3, 334; Keller-Schierlein, W.; Heilbronner, E. In "Non-Benzenoid Aromatic Compounds," Ginsburg, D., Ed.; Interscience: New York, 1959; Chapter 6, p. 277;
4. Nozoe, T.; Ito, S. *Fortschr. Chem. Org. Naturst.* **1961**, 19, 32.
5. Ziegler, K.; Hafner, K. *Angew. Chem.* **1955**, 67, 301;
6. Hafner, K. *Liebigs Ann. Chem.* **1957**, 606, 79.
7. Jutz, J. C. In *Top. Curr. Chem.* **1978**, 73, 125.

8. Sato, M.; Ebine, S.; Tsunetsugu, J. *Tetrahedron Lett.* **1974**, 2769;
 9. Copland, D.; Leaver, D.; Menzies, W. B. *Tetrahedron Lett.* **1977**, 639;
 10. Severin, T.; Ipach, I. *Synthesis* **1978**, 592;
 11. Mukherjee, D.; Dunn, L. C.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 251; Gupta, Y. N.; Mani, S. R.; Houk, K. N. *Tetrahedron Lett.* **1982**, 495.
 12. Nozoe, T.; Seto, S.; Matsumura, S.; Murase, Y. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1179, 1990;
 13. Oda, M.; Kitahara, Y.; *J. Chem. Soc., Chem. Commun.* **1969**, 352;
 14. Ehntholt, D. J.; Kerber, R. C. *J. Chem. Soc., Chem. Commun.* **1970**, 1451;
 15. Yang, P. W.; Yasunami, M.; Takase, K. *Tetrahedron Lett.* **1971**, 4275.
 16. König, W.; Regner, W. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 2823;
 17. Malhotra, S. S.; Whiting, M. C. *J. Chem. Soc.* **1960**, 3812.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

alumina

5-dimethylamino-2,4-pentadienylidenedimethyliminium perchlorate

hexanes

hydroazulenes

6-(4-methylanilino-1,3-butadienyl) pentafulvene

6-dimethylaminopentafulvene

6-acyloxypentafulvenes

hydrochloric acid (7647-01-0)

methanol (67-56-1)

magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

diethylamine (109-89-7)

[dimethylamine \(124-40-3\)](#)

[1-chloro-2,4-dinitrobenzene \(97-00-7\)](#)

[benzidine \(92-87-5\)](#)

[N-Methylaniline \(100-61-8\)](#)

[hexane \(110-54-3\)](#)

[Azulene \(275-51-4\)](#)

[CYCLOPENTADIENE \(542-92-7\)](#)

[dicyclopentadiene \(77-73-6\)](#)

[calcium hydride \(7789-78-8\)](#)

[thiophene 1,1-dioxide](#)

[1-diethylaminobutadiene](#)

[N-\(2,4-Dinitrophenyl\)pyridinium chloride](#)